DIP #606

Drug Interactions For The USMLEs (Step 1-3)

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- **Dr Mohammed Zaki**
https://chat.whatsapp.com/L6dShASc3f97cwHZgCD6Xo

- All right. Welcome to episode 606 of the **Divine Intervention Podcasts**.
- Into these podcasts, we're going to be examining a topic that is extremely, **extremely, extremely high-yield** for the **USMLEs**.
- You will see this material on your exams.
- You don't study it, you're doing it basically at your own risk.
- I'll try to see if I can compress everything into one podcast, but if I cannot, there'll be a **Part 2**.
- And this podcast is going to focus on **drug interactions**, **high-yield drug interactions**.

- OK, high-yield drug interactions.
- They love to test this stuff on **Step 1**, **Step 2 CK**, **Step 3**, **Level 1**, **Level 2**, **Level 3**.
- You will see this material on your exams.
- You need to know this.
- There is no ifs, no ands, no buts about it.

Warfarin

- All right, so let's begin.
- So what if they give you a question about a person that has **valvular Afib**, and then the person was given an **antibiotic**, and as this person was taking this antibiotic, you notice that they started **bleeding from their nose**?
- They started having **Gum bleeding**, and you check their **INR**, and their INR has gone up significantly.
- Well, what's going on here?
- Well, this is clearly **warfarin toxicity**.

- The thing is, warfarin has so many interactions, it's ridiculous how many interactions they have, like literally.
- You can make almost like 10 different **warfarin drug interaction questions** on your exams.
- So you may wonder, "Well Divine, in the vignette you just said, the person was not on warfarin. How did you get to warfarin?"
- Well, the person happens to have what is known as **valvular Afib**.
- They have **Afib** that involves a **valve problem**.

- Remember, whenever a person has **Afib**, they have to be on **anticoagulation**, that's a rule.
- You should basically sear it in your mind for the **USMLE**: If you have **Afib**, you need to be on **anticoagulation**.
- Now, if you have **Afib** that's from a **valvular reason**, right, like **mitral stenosis** or whatever, or you have like a **prosthetic valve** and you have **Afib**, you need to be on **warfarin**.
- **Warfarin** is pretty much your only option on the **USMLE exams**.

- So the thing is, there are **many, many drugs** that can interact with **warfarin**.
- So they can be... You will classically make it a person that is **chronically on warfarin** for whatever situation.
- And then you place them on some kind of drug.
- Usually it's going to be an **antibiotic**, and it's gonna raise their **warfarin levels**, right.

- So one key thing to know for the **USMLE** is for **warfarin**: What are these drugs that interact with it and what are the mechanisms, right?
- Like, for example, one classic **antibiotic issue** on your exams, probably the most common ones, is going to be a **macrolide**.
- **Macrolides**, they inhibit this enzyme known as **CYP3A4**.
- **CYP3A4** is an enzyme that helps us break down and metabolize **warfarin**.

- So if you take a **macrolide** and you take **warfarin** and you're already on **warfarin**, you will inhibit the metabolism and breakdown of **warfarin**.
- So you're going to have **high warfarin levels**.
- That's going to cause you to get in trouble, right.

- Another **antibiotic** you may see on your exam that can cause **warfarin toxicity** is a **fluoroquinolone**, right.
- **Fluoroquinolones**, they inhibit a **cytochrome P450 enzyme** known as **CYP1A2**.
- **CYP1A2** is one of those enzymes that help us break down **warfarin**.
- When you shut down **CYP1A2**, that's also going to reduce the metabolism of **warfarin**.

- That can actually raise your **warfarin levels**, and that can cause problems.
- And actually, one other thing that **fluoroquinolones** do that's kind of high-yield to know with **warfarin metabolism** is that **fluoroquinolones**, they **displace warfarin from albumin**.

- Because **albumin** is a big protein we find in the bloodstream, it's like a **carrier protein** for many things.
- One thing it carries is **warfarin**, right.
- So if you displace **warfarin**—because remember many times when something is **bound to albumin**, it doesn't necessarily do what it's supposed to do in the body.
- It's almost like you put it in this **neutral pool**.

- But when you **displace it from albumin**, it becomes more—it becomes **active**, and then you begin to have a **drug effect**.
- So that's another mechanism behind **fluoroquinolones** causing problems.

- Another **antibiotic** you may see with **warfarin** is **trimethoprim-sulfamethoxazole (Bactrim)**.
- **Bactrim** inhibits an enzyme known as **CYP2C9**.
- **CYP2C9** literally breaks down **warfarin**, right.
- So again, if you take **Bactrim**—**trimethoprim-sulfamethoxazole**—and you're already on **warfarin**, you can get in trouble and raise **warfarin levels**, right.
- And also, **Bactrim displaces warfarin from albumin**.

- Many resources, for whatever reason, do not talk about this, but this is actually something that is **pretty high-yield to know**.
- This **CYP2C9 enzyme** that I discussed with **warfarin**—that enzyme also is **inhibited by metronidazole**.

- So again, if you are taking **metronidazole** and you're taking **warfarin**, again, you can really raise your **warfarin levels**.
- So do you see why these days we prefer more of these **novel oral anticoagulants**?
- Because they have **fewer of these problems** compared with **warfarin**.

- But again, there are **certain situations** where **warfarin** is pretty much your **only bet**, especially if you have **valvular Afib**.
- That's like a **very high-yield indication** to know for your exams.
- Or they may just give it to a person because they want to **test the drug interaction**.
- And **warfarin** is also **pretty cheap**, even if it has all these issues, right.
- So you already know the **cost of health care** in this country and **insurance** and all those fun things.

- All right, now one other thing I just want to say in general, in general, in general with **warfarin** is that in general, when you take **antibiotics** with **warfarin**, you're kind of going down a **slippery slope**.
- Let me explain why.
- How does **warfarin** work?
- We know that **warfarin** works by **inhibiting vitamin K epoxide reductase**.

- When you hear **vitamin K epoxide reductase**, you're going to decrease the **gamma-carboxylation** and activation of your **clotting factors**—**Factors 2, 7, 9, and 10**, and I guess some proteins like **protein C and S**.
- Now, what do you think **vitamin K epoxide reductase** uses as a **cofactor**?
- I wonder why, I wonder what it will be.
- It's gonna be **vitamin K**.

- And **vitamin K** is made in the body by **gut flora**.
- So if you take **antibiotics**, you will kill off a lot of your **gut flora**.
- When you kill off a lot of your **gut flora**, you're killing off a lot of your **vitamin K production** in the body.

- If you kill all **vitamin K production**, that's a problem.
- Because if you're on **warfarin**, **warfarin** is inhibiting **vitamin K epoxide reductase**.
- But maybe there is at least a little bit of **vitamin K epoxide reductase** working, right, even in the presence of **warfarin**.
- But if you kill off the **source of vitamin K**, aka your **gut flora**, then you won't have at least some **vitamin K** to activate the **vitamin K epoxide reductase** that at least may still be working in the presence of **warfarin**.

- So you're pretty much **potentiating the warfarin toxicity** because you are potentiating decreased activity of **vitamin K epoxide reductase**.
- Again, all these things are **very high-yield to know** for your exams, and many resources will emphasize this, but it's **extremely high-yield** to know for your tests.

- And then another thing I'm going to say—I promise I'm going to stop talking about **warfarin** in a moment here.
- They can give you a question about a person that's on **warfarin**, and then they've been having **headaches** or they've been having **chronic joint pain**, and they've been taking **acetaminophen** often for their joint pain.
- And then they start having all these **bleeding complications**.
- Well, think of **acetaminophen**, right.
- Think of **acetaminophen**.

- **Acetaminophen** can also interact with **warfarin**.
- Many know that **acetaminophen** is something that can **destroy the liver**.
- And the **metabolite** that destroys the liver, hopefully, is called **NAPQI**.
- **NAPQI** is very, Liver destructive.
- That's the thing that primarily messes up the **liver** in **acetaminophen toxicity**.

- Now, the thing is—and many times, you're like, “Oh, let’s use **N-acetylcysteine** to help us with that”—but **NAPQI** also has another **destructive purpose**.
- **NAPQI** has the ability to **inhibit vitamin K epoxide reductase**.
- **NAPQI** literally can **inhibit vitamin K epoxide reductase**.
- When you shut down **vitamin K epoxide reductase**, you're going to potentiate basically **warfarin toxicity**.
- Because again, we know that **warfarin**, the way it works, is by **inhibiting vitamin K epoxide reductase**.
- OK, what if your body remakes some new **vitamin K epoxide reductases**, and at least that's kind of balancing out **warfarin's anticoagulant effect**.
- But if you bring something else on top that shuts that down, that can get you in a lot of trouble.

NSAIDs / Aspirin / ARBs/ ACEi

- Another classic **drug interaction** our friends at the **NBME** love to test is they can give you a question about a person that is on **chronic pharmacotherapy** for **osteoarthritis**, and then the person is also diagnosed with **hypertension**, and they start an **antihypertensive**, and then their **creatinine** rises a lot.
- When you see that kind of presentation, what should you be thinking about?
- Well, I hope you're really thinking about the **interaction between an NSAID and an ACE inhibitor or an ARB**.

- So remember, **NSAIDs**—or like even **aspirin**—because think about it, what are the people that may be taking **aspirin** and an **ACE inhibitor** together?
- Huh? Gee, it's going to be people that have **heart failure**.

- Let's say they have their heart failure from an **ischemic cardiomyopathy**,
- Well, if you think about it, people that have had like **ischemic cardiomyopathy**, like an **MI**, they have to be on **aspirin**.
- They have to be on **aspirin**—many times, they're going to be on that **aspirin indefinitely**,

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- Or at least they can be on it for the first **12 months** after they have had a **stent** placed in their hearts, right.
- But again, many times, they're going to be on it indefinitely.
- Well, **aspirin** or an **NSAID**, right. Again, I'm bringing in **NSAIDs** here.

- Typically, if a person has had a heart attack, you can put them on **aspirin**, not an **NSAID**, right.
- But they kind of do the same thing, right?
- **Inhibit cyclooxygenase**.

- When you **inhibit cyclooxygenase**, you're going to decrease the production of **prostaglandins**.
- When you decrease the production of **prostaglandins**, that's going to cause **constriction of the afferent arteriole**, because **prostaglandins dilate** the **afferent arteriole**.

- But if you shut down **prostaglandin synthesis**, you're going to lead to **constriction** of the **afferent arteriole**.
- When you constrict the **afferent arteriole**, that’s going to reduce **perfusion** of the **glomerular capillaries**.
- That's going to reduce the **hydrostatic pressure** within your **glomerular capillaries**.
- If you reduce the **hydrostatic pressure**, that's going to **lower the GFR** because you're going to have **less filtration**, and that's going to raise your **creatinine**.

- But if you then add another **risk factor** on top that can **lower your GFR**, like an **ACE inhibitor** or an **ARB**, that can get you in trouble.
- Well, how does that happen?
- Well, remember, **ACE inhibitors** and **ARBs**, right, they basically **downregulate** the activity of **angiotensin II**.
- **Angiotensin II** is a very **potent efferent arteriolar constrictor**.

- So if you give an **ACE inhibitor** or an **ARB** and you downregulate **angiotensin II** activity, you're going to **dilate your efferent arteriole**.
- It's not going to be constricted anymore.

- And if you **dilate your efferent arteriole**, that is going to draw blood away from your **glomerular capillaries**.
- If that happens, you're going to have **less hydrostatic pressure** within your **glomerular capillaries**.
- That is going to cause your **creatinine to rise**.

- Because again, your **GFR is being reduced**.
- If you reduce **hydrostatic pressure** within your **glomerular capillaries**, you're going to **reduce your GFR** because you're reducing **filtration**, and that's going to **raise your creatinine**.

- In fact, this thing I just explained is why **ACE inhibitors or ARBs**, they can normally raise your **creatinine** by a little bit when you start them.
- But it **shouldn't be raised by more than 30%**.

- But when you have another **risk factor** on top, like an **NSAID** or **aspirin**—two things combinatorially that can **decrease GFR**—that can get you in a lot of trouble.

- And you notice I try to emphasize the **mechanisms** behind the **GFR decreases**.
- They're kind of different depending on what you're dealing with.
- **ACE inhibitors/ARBs**: they **dilate the efferent arteriole**.
- **Aspirin and NSAIDs**: they **constrict the afferent arteriole**.

OCPs / Rifampin / Rifamycin

- Now remember, what if they give you a question about a patient?
- They tell you that she's a **27-year-old female** and that she missed her **period**.
- And you're told that oh, she was recently started on some kind of—she's a **healthy female**, she has been on **OCP**, but she was recently started on some kind of...
- She traveled to a **foreign country**, and then a **TB skin test** when she returned was **positive**, right.

- And then now she has basically **missed her period**, and you're told that **urine pregnancy test** is **positive**.
- She was also started on like maybe **latent TB therapy** or whatever.

- Why did this person get **pregnant**?
- Well, think of **OCPs** and **interactions**.
- Think of **OCPs** and interactions with **cytochrome P450 inducers**
- This is **very, very, very, very high-yield** to know for your exams.

- In general, taking an **OCP** and a **cytochrome P450 inducer** is **not a good idea**.
- And the one they most frequently love to test this with is with **rifampin**, right.

- **Rifampin** or **rifamycins**—basically **rifampin**, **rifamycin**—they **induce cytochrome P450 enzymes**, especially **CYP3A4**.
- **CYP3A4** is a very critical enzyme that helps us **break down OCPs**.

- So the thing is, if you take a **CYP3A4 inducer** while you're taking an **OCP**, then you will increase the amount of **CYP3A4** in the body.
- You have **more accelerated metabolism** of that **OCP**.
- As you have more accelerated metabolism of that **OCP**, guess what's going to happen?
- Your **OCP levels** are going to **fall**.
- You're pretty much **decreasing the half-life** of that **OCP**.
- That's going to cause you to **get pregnant**.

Vitamin D / Rifampin

- They can literally give you this exact same kind of vignette in a person that has **vitamin D deficiency**, and you're giving them **vitamin D supplementation**,
- But that **vitamin D supplementation** they're getting **doesn't seem to be working**.
- It doesn't seem to be helping.
- The **vitamin D levels** in the body are **not rising**.
- Well, again, if you **induce cytochrome P450 enzymes** with a **cytochrome P450 inducer**,
- That can cause you to get in a lot of trouble—right, especially **rifampin**.

- That can cause you to get in a lot of trouble because you have **accelerated metabolism** of **vitamin D**,
- So you will basically be getting **little, if any, effect** from that **vitamin D**.

Antacid / Levothyroxine / Fluoroquinolones / Tetracyclines

- What if they give you a question about a person?
- They tell you that this person has a **history of GERD**, and the person has been on **pharmacotherapy**,
- And this person was recently diagnosed with **Hashimoto's thyroiditis**.

- And you're told that the person was placed on **pharmacotherapy** for **Hashimoto's**,
- But at the person—their **follow-up visit**, like **3 months later**, they still continue to complain of **symptoms**.
- And you are told that their **TSH** is still **markedly elevated**.
- What's the mechanism behind the **side effect** that they have or behind their **failed response** to **levothyroxine**?
- It’s because of **reduced bioavailability**.

- Pick the answer that talks about **reduced bioavailability**.
- So what's the mechanism there?
- Well, if you really think about this, this person has **GERD**.
- This person has **GERD**.
- Well, if you have **GERD**, chances are you're taking some kind of **antacid**.

- The problem with **antacids** is that **antacids love to chelate stuff**.
- They love to chelate stuff in the **GI tract**.
- They love to chelate things like **levothyroxine**.
- They love to chelate things like **tetracycline**, right.
- They love to chelate things like **fluoroquinolones**.

- So you will not get any effect from those drugs if you're taking them and you're taking an **antacid** at the same time.
- So that's why this person is not responding to **levothyroxine therapy**—
- Because that **levothyroxine** is being **chelated**.

- So you're reducing the **bioavailability** because it is not being **reabsorbed into the bloodstream**.
- It is not being **reabsorbed into the bloodstream**.

- So please, they can literally write the same vignette in a person that's taking a **tetracycline** for like **Lyme disease**, and they're **not getting better**,
- Or they're taking a **tetracycline** for some other purpose and they're **not getting better**,
- Or a person that's taking a **fluoroquinolone** for some purpose and they're **not getting better**.

- Again, **levothyroxine**, **fluoroquinolones**, and **tetracyclines**,
- They get **chelated** by these **antacids**.
- Please, this is **very, very high-yield** to know for your exams.

- And I guess I can throw in a plug here for **antacids**, especially these **divalent ions**, like **calcium**, for example.
- Remember, **calcium**—we find a lot in **bones**.
- And that actually explains the **mechanism** behind how **tetracyclines** can cause a lot of **bone problems**, right.

- Because there's a lot of **calcium in bones**, **tetracyclines** really, really love to **bind to calcium**.

Nitrates / Sildenafil

- OK. Now what if they give you a question about a patient?
- They tell you that this patient has a history of **atherosclerotic cardiovascular disease**.
- The person is on **pharmacotherapy** for **angina**, right.

- But that the person has been having **marital problems** with his... with his **wife**,
- And he was placed on a **pharmacotherapy** for **erectile dysfunction**,
- And then now this person, whenever they rise out of bed in the morning,
- That they've had like **one or two falls**,
- And then they can say, “Which of the following is the most likely **mechanism** behind the patient’s increased **propensity to falling**,” right, or something along those lines.

- Well, if you think about that, you want to think about the combination of **sildenafil** and a **nitrate**.
- **Sildenafil** and a **nitrate**.

- So the person is probably on **nitrates** for their **angina**,
- And then that **nitrate** causes a lot of... remember, **nitrates** are **venodilators**.
- They’re **very potent venodilators**.
- So they can **crush your preload**.
- They can literally do what?
- They can literally **crush your preload**.

- When you **crush your person’s preload**, you’re **reducing the amount of blood going back to the heart**.
- That’s going to **reduce their cardiac output**.
- If you reduce your **cardiac output**, that can cause **hypotension**.

- Now, we know that **sildenafil** is a **phosphodiesterase-5 inhibitor**.
- When you **inhibit phosphodiesterase-5**, you're going to increase **cyclic GMP activity**, right.
- When you **facilitate cyclic GMP activity**, **cyclic GMP** leads to a lot of **vasodilation**.

- So when you’re **combining those two things** that are **very vasoactive agents**,
- That can cause your **blood pressure** to **drop significantly**,
- Cause your blood pressure to **drop** and that can throw you into **orthostatic hypotension**, right.

- So they can test **orthostasis** with that,
- Or they can test the person that whenever they **rise out of bed**, they just **collapse to the ground**,
- Because they have **decreased perfusion of the brain**.
- Again, that **interaction** is **very, very high-yield** to know for your exams.
- But I think another **interaction** that's useful to discuss is between **sildenafil** and **cytochrome P450 inhibitors**.

- **Cytochrome P450 inhibitors**, especially **cimetidine**, especially **erythromycin**,
- And also like your **-azoles**, like **itraconazole**—
- Those things can **shut down the breakdown** of **sildenafil**.
- They can **shut down the breakdown** of **sildenafil**, and that can **raise your sildenafil levels**, right.

- Because again, they know that, “Oh, everybody knows **sildenafil plus a nitrate** = unsafe, **drop in blood pressure**, don’t do that.”
- But if you're taking **sildenafil** and you're taking a **cytochrome P450 inhibitor**,
- Those can **raise your sildenafil levels**, and that can cause **sildenafil toxicity**.

Serotonin Syndrome

- Right now, what if they give you a question about a patient that is placed on...
- They give you a question about a patient that is on **pharmacotherapy** for **major depressive disorder** or **generalized anxiety disorder**,
- And then you're told that this person was recently started taking some kind of **herbal supplement**, right.

- And then the person presents to the **emergency room** because he's been having like **shaking of his hands**.
- You're told that he has like **increased deep tendon reflexes** and all those things and has **myoclonus**.
- When you see something like that, I would really, really hope you're thinking about **serotonin syndrome**, right.
- I really hope you're thinking about **serotonin syndrome**.

- They **love, love, love, love, love** to test **serotonin syndrome** on the exams because there are so many **interactions**.
- Many, many **drug interactions** that they can test with **serotonin syndrome**, right.

- Like, for example, they can test about a person that is taking an **SSRI** and also taking **St. John's Wort**.
- **St. John's Wort** is a **herbal supplement**, but it also has **pro-serotonergic properties**.

- It has **pro-serotonergic properties**. It can cause problems in people.
- That can absolutely cause **serotonin syndrome**.

- Or they can give you a question about a person that is taking an **SSRI**, right,
- And the person is on **Parkinson's disease therapy**, like a **monoamine oxidase inhibitor** like **selegiline**, for example, right.

- When you **inhibit monoamine oxidase**, you're gonna...
- **Monoamine oxidase** helps us **break down serotonin**, right.
- So if you're on an **SSRI** and then you take a **monoamine oxidase inhibitor** like **selegiline**, for example (used for **Parkinson's**),
- Or any **MAOI** that we use for **depression**, like **isocarboxazid**, for example—
- That can **raise your serotonin levels**.

- Because remember, by **inhibiting monoamine oxidase**, you will **stop breaking down serotonin**.
- So you're **raising serotonin levels** in the presence of you taking another drug like an **SSRI**—
- That can cause **serotonin syndrome**.

- Even they can give you a person that is already on an **SSRI chronically** for some **mood disorder**,
- But in addition to that, the person then starts an **antibiotic**.

- What **antibiotic** is going to raise your **SSRI levels**?
- I mean, what **antibiotic** is going to cause **serotonin syndrome**?
- Well, think of **linezolid**, right.

- They can give you a person that has like a **MRSA infection**.
- **Linezolid**, **linezolid**, **linezolid**, **linezolid**, **linezolid**, **linezolid**.

- What does **linezolid** do?
- **Linezolid** is a **monoamine oxidase inhibitor**.
- Remember, it's a **50S inhibitor** that can cover **MRSA** very well and **vancomycin-resistant Enterococcus**.

- But it also **inhibits monoamine oxidase**.
- So it can **decrease the metabolism of serotonin**, and that can get you in a lot of trouble.

- Alright, now what are some other **SSRI interactions** to know?
- Again, with **serotonin syndrome**.
- Well, think about **SSRIs and tramadol**.
- **SSRIs and tramadol**, **tramadol**, **tramadol**, **tramadol**, **tramadol**, **tramadol**, **tramadol**.
- **Tramadol** has **serotonergic activity**.
- Again, if you **combine it with an SSRI**, you can get in a lot of **hot water**.

- Another **interaction** to also keep in mind is like an **SSRI and triptans**—like **sumatriptan**.
- Remember, **sumatriptan** is used for **migraines**.
- How do **triptans** work?
- Well, **triptans** are **serotonin receptor agonists**.

- If you **combine them with an SSRI**, that can absolutely, positively raise your risk of **serotonin syndrome**, right.
- Again, please, all these things—this is a **very detailed podcast**, but this is a **very, very high-yield podcast** to know.

- And it's not enough to just know the **interaction**.
- You need to know the **mechanism** behind the **problems that you face**—

- In fact, one thing I forgot to say when I was talking about **SSRIs**—
- The **SSRIs**, and again, all the **serotonergic things**,
- Like combining an **SSRI** and an **SNRI**,
- Or combining an **SSRI** and an **MAOI**,
- Or combining an **SSRI** and a **tricyclic antidepressant**—
- That can absolutely **get you in trouble**: **serotonin syndrome**.

Statins/ Fibrates

- Now what if they give you a question about a patient that has been on **statin therapy** for the longest time,
- And then the person is placed on another **lipid-lowering medication** in addition to the **statin**,
- And then you're told the person has been complaining of a lot of **myalgias**, and the **creatine kinase** is **elevated**?
- Well, think of **statins and fibrates**.

- The thing is, it is **very high-yield** to know this:
- That if you're already on a **statin**, taking a **fibrate** in addition to that is **not a good idea**.

- Why? Because **fibrates**, they can **shut down the breakdown**—
- Basically, **statins and fibrates**, they can **shut down the breakdown of each other**.
- So that can **raise the levels** of each, right—especially **fibrates**.
- Especially **gemfibrozil**.
- **Gemfibrozil** is a **very, very big culprit** here.
- It can **raise your statin levels**, right.

- And if you **raise the statin levels**, you can increase the person's risk of **rhabdomyolysis**.
- Remember, **statins can cause a myopathy**.

- And then there's this **enzyme** that breaks down **statins**.
- It's known as **OATP1B1**.
- **OATP1B1** is inhibited by **macrolides**, especially **clarithromycin**.

- So if you're taking a **statin** and you're taking **clarithromycin**, for example—a **macrolide**—
- That can **shut down the breakdown** of those **statins**,
- You can **raise your statin levels**, and you can **get in a lot of trouble**.

Statins.

- And the thing is, they love to test these particular **drugs** because these **drugs are commonly used in medicine**, right.
- They are **very widely used**.
- How many people are **not on statins** in this country, right?
- Or even **worldwide**, right.

- So **statins** also can actually—
- So if you're taking a **statin** and **warfarin**,
- That can actually cause **problems**.

- **Statins and warfarin** actually interact.
- **Statins and warfarin** actually interact.
- Well, how do they interact?

- Well, the thing is, see **CYP2C9** and **CYP3A4**—
- They both **break down statins** and **warfarin**.
- So it's like, oh—**statins**, **CYP2C9**, **CYP3A4**,
- That breaks down **statins**, right.
- But also, **CYP2C9**, **CYP3A4**, also breaks down **warfarin**.

- So you have **competition**.
- You have these two **drugs** that are broken down by the **same kind of enzymes**,
- By the **same kind of cytochrome P450 enzymes**.

- So if you're taking these two **drugs** at the same time—which is **not uncommon**—
- There are many people that are on **warfarin** and on a **statin**.
- But we're trying to **prevent that** these days in healthcare, right.

- They're **competing for breakdown**,
- So it's obvious—one is going to be **broken down more** than the other.
- And the one that is **not broken down as much**, you're going to **raise levels** of that thing—
- Especially **warfarin**.

- Especially **warfarin**.
- And that can cause your **INR to rise up**, right.

Anti-epileptic drugs

- Now let's talk about the world of **anti-epileptic drugs**.
- Especially **carbamazepine**, **phenytoin**, and **phenobarbital**.

- I kid you not—they **love to test** these **anti-epileptic drugs** and how they can **interact with many other things** on the **USMLEs**.
- See, there are many—there's like lots and lots of **drug interactions** we can talk about today.

- But again, I'm literally just focused on the ones that **characteristically show up** on the **USMLE exams**, right.
- So what are some **classic ones** to know?
- Basically, if you're taking an **anti-epileptic drug**, and something—
- And something that **inhibits cytochrome P450**—
- That can **raise those anti-epileptic drug levels**.

- It can **raise those levels**.
- So the thing is, there are many **cytochrome P450 inhibitors**,
- But what are the **classic ones** they love to test on the exams?

- They love to test **cimetidine**.
- They love to test **macrolides**, especially **erythromycin** and **clarithromycin**.
- And they also love to test **fluconazole**.

- OK, so don't get me wrong—there are many **cytochrome P450 inhibitors** to know for your tests.
- But these are the **classic ones** they love to test in the context of **drug interactions**:
    - **Cimetidine**
    - **Erythromycin**,
    - **Clarithromycin**,
    - **Fluconazole**.

- These things are **very important cytochrome P450 inhibitors**.
- When you **inhibit cytochrome P450**, you're going to **shut down the metabolism**—
- Right, the **breakdown** of **anti-epileptic drugs**.

- Especially which ones?
- **Carbamazepine**,
- **Phenytoin**,
- **Phenobarbital**.

- You can **potentiate the effects** of those drugs.
- You can have a lot of **toxicity** with those drugs.

- Now on the **flip side**, on the **other edge of things**,
- How about **anti-epileptic drugs** and **lowering their levels**, right?
- They will classically give you questions in people that are taking one of these **anti-epileptics**,
- And then you notice that they start having **more frequent seizures**.
- Like they'll tell you that, "Oh wow, their **seizures** have been **well-controlled** for the longest time."
- And then out of the blue, they start having **seizures**.
- And then they tell you that, "Oh, this person recently started taking some kind of **medication**."

- Well, the thing is, if you take an **anti-epileptic drug** and a **cytochrome P450 inducer**—
- A **cytochrome P450 inducer**, right—
- That's going to **accelerate the metabolism**,
- **Accelerate the breakdown** of these **anti-epileptics**.

- You're going to **lower these anti-epileptic drug levels**, and that's going to cause problems.

- Again, what are the classic **anti-epileptics** they love to test with these?
- They love to test this with:
    - **Carbamazepine**,
    - **Phenytoin**,
    - And **phenobarbital**.

- **Phenobarbital** is probably **less frequently tested**,
- But **carbamazepine** and **phenytoin**—oh my goodness—
- They **love, love, love, love, love** to test those things.
- So please make sure—
- Please make sure you **know those drug interactions**, right.

Lithium / Diuretics

- Alright. Now, one other **interaction** I want to talk about.
- Right—you can give a question about a person.
- And this person is on a **mood stabilizer**,
- And then they were recently diagnosed with **hypertension**, and they were placed on an **antihypertensive**,
- And then you notice that, "Oh, this person has now been having **tremors**,"
- They've been having **altered mental status**, and all these things.

- Well, what **drug interaction** do you want to think about?
- You want to think about a person that's taking a **diuretic** and taking **lithium**, right.
- You can cause **lithium toxicity** when you're taking a **diuretic**.

- So what's the **mechanism** behind the **diuretic causing lithium toxicity**?
- It's actually kind of straightforward.
- But actually, this is **very high-yield** to know for your exams.

- See, how does the body work?
- See, the body—one place that the body **reabsorbs sodium and lithium** in is in the **proximal tubule**.
- This is something many resources don't cover.
- This is something many people do not know.
- But **sodium and lithium**—they are absorbed in many parts of the **kidney**,
- But for purposes of our discussion, I want you to know that **lithium and sodium** are **reabsorbed in the proximal tubule**.

- And the thing is, if you think about it, there are not many **diuretics** that work in the **proximal tubule**, right.
- Most **diuretics** work in more **distal parts of the nephron**.

- So like, for example, what's like probably one of the more common **diuretic classes** that are taken for people that have **high blood pressure**?
- It's going to be a **thiazide diuretic**.
- **Thiazide diuretics**—they work at the level of the **distal convoluted tubule** to inhibit the **sodium-chloride symporter**.

- Well, the thing is, if you start on a **diuretic**, those **diuretics** are going to cause you to become **volume depleted**,
- Because they are blocking **reabsorption of ions** in your **kidneys**.
- That's going to take water along with it, it's going to cause you to become **volume depleted**.
- Your body is not going to be happy with that.

- Your body is going to be like, “Man, why am I losing all these ions in the more **distal parts** of my nephron, like the **distal tubule**?”
- So your body is going to be like, “Huh, what? I will compensate.”
- “How am I going to compensate? I’m going to compensate by literally **reabsorbing more sodium** in the **proximal tubule**.”

- When you **reabsorb more sodium** in the **proximal tubule**, right—
- Then, even if you have these **drugs** that are inhibiting your **distal nephron**, it's not going to be a big deal anymore to you.
- You're going to be like, “Whatever, whatever, I'm good.”
- Why can you say that? Because now—now—
- You've gotten to a point where some of those **ions** that could have been wasted at the **distal nephron**—
- They have been **reabsorbed at the proximal tubule**.

- Right. That's why, after a while, like your body **adjusts**.
- Your body is a **very smart system**—God created a very good body, right.
- Your body **adjusts** to those **diuretics**.
- They still work—they still work, don't get me wrong.
- They’re still effective.
- But again, your body begins to **compensate** by reabsorbing more of that **sodium** in the **proximal tubule**.

- But the thing is, **sodium and lithium** are pretty similar.
- If you remember back to **general chemistry** from college—
- **Sodium and lithium**, they are both in **Group 1** of the **periodic table**.
- So many **transporters** that can help with **sodium reabsorption** can absolutely help with **lithium reabsorption**.

- In fact, let me tell you this. Let me tell you something—
- **Lithium is smaller than sodium**.
- So because **lithium is smaller than sodium**,
- If **sodium** can go through a **transporter** really well,
- Do you really think that **lithium** cannot go through that **transporter** as well?
- It **absolutely can**.

- So when your body is compensating for that **diuretic**,
- When your body is compensating for that **diuretic** by **increasing sodium reabsorption** in the **proximal tubule**—
- Well, guess what?
- You're also having **increased reabsorption of lithium**.
- And as you **increase the reabsorption of lithium**,
- You're going to **increase your risk of lithium toxicity**.
- That is **very, very, very, very high-yield** to know for your exams, right.
- Because as more **lithium** is **reabsorbed**, you can have more **toxicity**.

- Now the thing is, you can actually **broaden**—
- You can actually **broaden your application** of this principle.
- Basically, **states of volume depletion** can **raise your risk of lithium toxicity**.
- Because again, when you have a **state of volume depletion**, you're going to have **increased sodium and lithium reabsorption** at the **proximal tubule**,
- Because your body is trying to **hold as much sodium as possible** so it can **hold as much fluid as possible** to counteract that **volume depletion** that you have, right.

- So if a person is **dry for whatever reason**—let's say they have **hypovolemic shock**, and they're on **lithium** as a **mood stabilizer**—
- They can have **lithium toxicity**.

- So make sure you can **make these integrations**.
- Make sure you can **put all these things together**.
- These things are **very, very important to know** for your exams.

- This podcast is probably like—I can probably put it in like a **top 20 podcast** that I've made.
- I've made a lot of **high-yield podcasts** in my life, but this one is **pretty high-yield**.
- You're going to see this stuff on your **exams**.
- And this is one of those things—
- There is **no test-taking strategy** that will prepare you for it.
- You either **know it or you don't know it**.

- This is—I would almost equate the importance of this podcast to **almost as important** as my **Risk Factors Podcast**,
- Which, as you know, is like **super, super, super high-yield**.

Trimethoprim-Sulfamethoxazole / Hyperkalemia

- So many of you know that the **principal cell** of the **collecting duct**, right—
- **Sodium** gets **reabsorbed through that ENaC channel**, and that **triggers the excretion of potassium**.

- If you **shut down that system**, that can cause **problems**,
- So like **Bactrim**, for example—**trimethoprim-sulfamethoxazole**—
- **Shuts down that ENaC channel**.

- If you **shut down that ENaC channel**,
- You're going to **stop excreting potassium**.
- You're really going to **stop excreting potassium** into the **urine**.
- That's going to **raise your serum potassium levels**,
- And you're going to have **hyperkalemia**, right.

- So **Bactrim** is an **ENaC channel blocker**.
- By **blocking ENaC channels**, that's going to **reduce the excretion of potassium** in the **kidneys**,
- And that's going to cause you to **retain more potassium**.
- That's going to cause **hyperkalemia**.